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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/697,863	10/27/2000	Stefan M C Pype	4555US	7540

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TRASK BRITT
P.O. BOX 2550
SALT LAKE CITY, UT 84110

EXAMINER
LIU, SAMUEL W

ART UNIT	PAPER NUMBER
1653	15

DATE MAILED: 05/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/697,863	PYPE ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *24 March 2003 (Papepr No. 14)* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,6,19,20 and 23-25* is/are pending in the application.

4a) Of the above claim(s) *3 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,19,20,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *PCT?EP 99/03025* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The response filed 24 March 2003 (Paper No. 14) as to amendment of claims 1, 6, 19 and 20 has been entered. Note that claims 8-10, 12-18 and 22 (see Applicants' amendment filed 11 April 2002, Paper No. 10) and claims 2, 4, 7, 11 and 21 (see Applicants' amendment filed 8 May 2001, Paper No. 5) are cancelled, and note that claims 3 and 23 are withdrawn from consideration by examiner as being drawn to non-elected sequence of SEQ ID NO:4. Thus, claims 1, 5-6, 19-20 and 24-25 are pending to which the followings are or remain applicable. Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Claim Rejections - 35 USC § 112, the first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5, 6, 19-20, and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification while being enabling for the isolated full-length amino acid sequence of CD40 interacting protein, *i.e.*, TTRAP (TRAF and TNF receptor associated protein) SEQ ID NO:2, does not reasonably provide enablement for all polypeptide variants having 70-100%

homology to or a fragment of SEQ ID NO:2, and a pharmaceutical composition comprising the polypeptide variant thereof, or, pharmaceutical composition comprising a compound characterized by interfering with interaction between the fragment thereof and protein factors involved in CD40-mediated signaling pathway. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification is insufficient to enable a skilled artisan to practice the invention as broadly claimed without an undue amount of experimentation.

Applicant is in possession of the full-length polypeptide SEQ ID NO:2. Applicant is not in possession of any isolated variant molecules including naturally-occurring allelic variants (see page 7, lines 9 to page 8, line 2) and recombinant mutants (see page 8, lines 1-2) or any peptide sequences having about 70% homology to SEQ ID NO:2; any variant molecules that are structural or functionally equivalent to the full-length SEQW ID NO:2 (note that the specification defines the "homology" as "the respective sequences are functionally and structurally equivalent"); and any derivatives (see page 8, line 3) that are structurally deviated from SEQ ID NO:2 sequence; any fragment or portion of the full-length sequences that are only 70-99% identical to the full-length SEQ ID NO:2; and any pharmaceutical composition comprising the fragment thereof; and any compound identified from screening interaction of the variant molecule with component(s) of CD40-mediated signaling pathway. The current claim language thus encompasses a large number of the polypeptide variants or fragments that are both structurally and functionally divergent from the disclosed full-length TTRAP polypeptide thereof.

The instant application does not provide guidance and working examples or representative example(s) as to structural and functional characterization of these variants. Absence of the guidance in the specification as to which ones would or would not have been a priori active or inactive, the current disclosure does not enable the skilled artisan to practice what the invention discloses. The claims as written encompass a large quantity of polypeptide fragments or variants or derivative including (*i*) a large number of possibilities in respect to the length of polypeptide that are structurally deviated from the full-length sequence SEQ ID NO:2, and (*ii*) a large number of mutational variants resulting from substitution, additions, deletions, fusion/chimeric, which are generated by mutagenesis techniques (See page 7, lines 29), and (*iii*) structural variants in any combination of the above mentioned mutations.

The claims of the instant application recite "having 70-100% homology" (see claim 1), wherein the homology *per se* is even broadened up to include any structural and functionally equivalent, e.g., genetic mutants and recombinant mutants (see the page 7, the last paragraph); such the claim language permits differences far beyond sequence identity in its face ranging from 1% to 30 %, *i.e.*, 99-70% sequence identity to the full-length sequence. Thus, the variant polypeptide molecules as claimed are far more divergent than 30 % sequence identity mutants, which would render the claimed polypeptide variant highly unpredictable.

The claims of the present invention also recite "a fragment comprising … of SEQ ID NO:2" (see claims 5-6), wherein the "comprising" is open-ended; such the recitation renders the claimed protein unpredictable because the specification is silent in description of the structural fragment thereof. Further, the current invention recites "a pharmaceutical composition

comprising a functional fragment of the claimed polypeptide (see claim 19, wherein the "functional fragment" includes any truncated sequences which encompasses the subsequences ranging from peptide consisting of 5 amino acid residues to polypeptide of 60 amino acid residues (see page 14, line 26 to page 15, line 6). Since 5 amino acids consists only of ~ 1.4% of total residues of SEQ ID NO:2 sequence (363 amino acid residues) whereas the specification is silent with respect to a minimum sequence (*i.e.*, core sequence or motif) for the TTRAP protein of SEQ ID NO:2 sequence, and since the specification does not teach or address the issue as to whether or not the truncated peptides of 5 to 60 amino acids retain the same or significant biological acidity of the full-length SEQ ID NO:2 polypeptide, the claimed "functional fragment" is highly unpredictable.

Because the specification fails to provide working examples or/and guidance or teaching with regard to make and use of the polypeptide variants stated *supra,* and fails to describe biological function of any representative member of the variant (genus), and because the present claim language, *e.g.*, about "70% homology to" and "a fragment comprising, render the claims so broad that the scope of claims is outside the bounds of the enablement, the current application would have resulted in the necessity of undue experimentation.

Description of invention reduction to practice, unaccompanied by any meaningful, distinguishing characteristics of the peptide variants stated above is insufficient to satisfy written description requirement of 35 U.S.C. §112, since inventors could have provided description of the variants or representative thereof of SEQ ID NO:2 polypeptide, since actual reduction to practice may demonstrate possession of embodiment of invention, but it does not necessarily describe what invention is, and since, in context of present case, disclosure of manner in which

invention was reduced to practice does not satisfy more fundamental written description requirement set forth in Section 112.

Applicant has disclosed only the polypeptide of SEQ ID NO:2; therefore, the skilled artisan cannot envision all the contemplated nucleotide sequence possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the variants to describe the claimed polypeptide derivatives including fragments, portions and mutants, and fails to provide written description regarding the biological activity or role(s) of the polypeptide variants. Thus, Applicant was not in possession of making and using the claimed polypeptides such as using the polypeptide fragment(s) in treating CD40, and/or tumor necrosis factor (TNF) receptor related disease states, *e.g.*, atherosclerosis, arthritis,

multiple sclerosis (see page 12, the first paragraph). *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

In consideration of the issue stated *supra*, the amount and level of experimentation needed is undue.

Response to the rejection under 35 USC 112, the first paragraph

The response filed 24 March 2003 comments that the claimed "homology" that includes various mutations are enable in supporting the current invention because SEQ ID NO:2 (362 amino acids) is of 70% sequence identity to murine SEQ ID NO:4 (371 amino acids) and because a possible TTRAP homologue from *C. elegans* which is 30 %identical to TTRAP as indicated in Example 8 (see page 11, the first two paragraphs). The response thus infers that the current disclosure has provided guidance that enables the skilled artisan to make and use the claimed fragment or variant of TTRAP (see the paragraphs at the bridging pages 12-13).

The applicants' argument is not persuasive. It is of note that the specification does not set forth that SEQ ID NO:2 is 70% identical to SEQ ID NO:4 sequence. Moreover, the specification provides neither working example nor teaching as to comparison of biological activity of polypeptide of SEQ ID NO:2 with that of polypeptide of SEQ ID NO:4. Thus, the argument based on 70% sequence identity between SEQ ID NOs: 2 and 4 is unpersuasive. As for as "a possible TTRAP homologue from *C. elegans* which is 30 % identical to TTRAP" is concerned, because the specification provides no factual evidence regarding the said *C. elegans*

protein. Note that the specification only sets forth an assumed homology between human TTRAP and invertebrate, i.e., nematode, protein, which are approximately 30% identical from each, and that the assumption is based on protein alignment; yet, without a support by experimental data, any 30% sequence similarity does not necessarily establish structural or/and functional homologue between the compared molecules, absent factual evidence to the contrary. Therefore, the applicants' argument is unpersuasive.

Also, the response comments that Table 1 of indicates an importance of the subsequence 274-362 of SEQ ID NO:2 for binding the TNF superfamily receptor, and page 4, line 18 indicates that the other subsequences, *e.g.*, amino acids 115-121, 145-153 and 347-352 are important for the binding thereof; thus, the instant claims are enable (see the response page 11, the last paragraph). The applicants' comment has been considered but it is not persuasive. The reasons for this are stated in the following.

The specification does not provide sufficient guidance and working examples for the subsequences, *e.g.*, amino acids 115-121, the specification (see page 4, line 18^{+}) is silent as to the factual evidence of binding of the subsequences (115-121, 145-153 and 347-352) to the TNF receptor or/and CD40 but identifies only amino acid compositions and sequences of these subsequences. Thus, the subsequences set forth in page 4, line 18^{+} does not support the enablement.

In regard to the subsequence (274-362) of SEQ ID NO:2, none of data on Table 1 shows the subsequence (274-362) having ability of binding to the listed protein factors of CD40-mdirtaed signaling pathway in comparison with wild-type TTRAP protein (SEQ ID NO:2). Thus, the specification provide no factual evidence to identify the sequence (residues 274-362).

Moreover, the specification defines "fragment" as a truncated sequence of, typically, 5 to 60 amino acid residues whereas the subsequence (274-362) consists of 88 residues; the claim language "a fragment" (claims 1, 5-6 and 19) does not the subsequence (274-362). Taken together, it is concluded that the specification does not provide representative working example in this regard and insufficient description to support the enablement.

Claim Rejections - 35 USC §102

This a new ground rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Green C. B. *et al.* (*Proc. Natl. Acad. Sci. USA* (1996) 93, 14884-14888).

Green *et al.* teach a polypeptide, *i.*e., nocturnin, (see Figure 10) which is a TTRAP homologue interacting with protein factors of CD40-mediated signaling pathway. The nocturnin polypeptide comprises an amino acid fragment (residues 367-371) homologous to the fragment (residues 347-351) of SEQ ID NO:2 of the current disclosure, which meets the limitation of "or a fragment thereof said protein…" set forth in claims 1 and 19 of the instant application .

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.

May 1, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER